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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Second Peer Review of Permethrin -- Consideration of Recommendations by the Scientific Advisory Panel Regarding the Oncogenic Classification of Permethrin

FROM: Edwin R. Budd *Edwin R. Budd*
Section Head
Toxicology Branch I (IRS) 8/16/89
Health Effects Division (H7509C)

TO: George LaRocca
Product Manager #15
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The Health Effects Division (HED) Peer Review Committee met on June 1, 1989 to consider comments and recommendations made by the FIFRA Scientific Advisory Panel (SAP) on May 9, 1989 with respect to the committee's previous classification of the carcinogenicity of permethrin.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

Penelope Fenner-Crisp

Reto Engler

Marcia van Gemert

Edwin Budd

Kerry Dearfield

George Ghali

Richard Levy

Esther Rinde

William Sette

Penelope A. Fenner-Crisp

Reto Engler

Marcia van Gemert

Edwin Budd

Kerry Dearfield

G. Ghali

Richard A. Levy



Esther Rinde

William Sette

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

John Doherty

Bernice Fisher

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the committee unless otherwise stated.)

William Burnam

Karl Baetcke

Robert Beliles

Marion Copley

Jack Quest


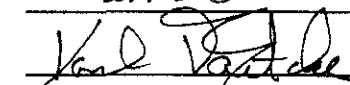
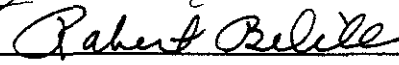
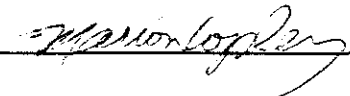

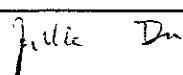
Richard Hill

Lynnard Slaughter

4. Other Attendants; (observers)

Robert Zendzian

Hugh Pettigrew

B. Material Reviewed:

The material available for review consisted of:

- (1) the final FIFRA SAP report on the May 9, 1989 meeting (memorandum by Robert Jaeger, dated May 16, 1989),
- (2) the final FIFRA SAP report on a previous meeting convened on March 10, 1981, to consider the oncogenic potential of permethrin (memorandum by Philip Gray, Jr., dated March 20, 1981),
- (3) the first HED "Peer Review of Permethrin" held on December 12, 1988 (memorandum by Esther Rinde, Ph.D, dated April 7, 1989),

- (4) comments on the need for quantitative oncogenic risk assessment (memorandum by John Doherty, Ph.D, dated June 1, 1989).

The material reviewed is attached to the file copy of this report.

C. Background Information:

In December 1988, the HED Peer Review Committee met to consider the oncogenicity data base for permethrin and to classify it according to the Agency's Carcinogen Risk Assessment Guidelines. Permethrin had not previously been considered by the Peer Review Committee. The conclusions reached at this meeting are presented below:

"The Peer Review Committee classified Permethrin as a Group C (possible human carcinogen), based on evidence in one species (mouse). The evidence in the second species (Long-Evans rat) was considered to be equivocal, but suggestive. The Committee also called for a quantitative risk assessment for Permethrin, based on: 2 tumor types (liver and lung) of which one (lung) was malignant, the dose-related response seen in the mouse, suggestive evidence in the Long-Evans rat, and supportive SAR information." [quoted from the memorandum by Esther Rinde, Ph.D., dated April 7, 1989.]

In May 1989, the FIFRA SAP met and commented on the Peer Review Committee's overall assessment of the weight-of-the-evidence and classification of permethrin. The Panel's comments are presented below:

"The Scientific Advisory Panel has reviewed the data base on the oncogenicity of Permethrin which consists of 3 rat and 3 mouse bioassays. In only one mouse study was any dose response manifested in lung tumors in the female (both adenomas and carcinomas). The compound was not mutagenic in a battery of bioassays. Accordingly, the Panel recommends that Permethrin be classified as a Category [sic] C Oncogen. However, because of the relatively weak tumorigenicity and the lack of mutagenicity data, the Panel does not recommend any quantitative risk assessment." [quoted from the memorandum by Robert Jaeger, dated May 16, 1989.]

Although the HED Peer Review Committee and the SAP both recommended that permethrin be classified as a Group C oncogen, the Peer Review Committee called for a quantitative risk assessment whereas the SAP did not.

D. Considerations:

It was noted by the Peer Review Committee that the most recent (1989) recommendation by the SAP regarding the oncogenic potential of permethrin was quite similar to an earlier (1981) "advisory opinion" by the SAP on the oncogenic potential of permethrin, which reported the panel's recommendations following a public meeting in March 1981. The panel's 1981 overall assessment of the oncogenic potency of permethrin is presented below:

"The ICI [sic¹] and FMC Mouse II studies suggest that there may be a very small possibility of carcinogenic potential of Permethrin in mice. Coupled with the rat studies, this suggests a very limited potential and/or potency, or none at all. The Panel thus expressed the view that, based on all the data together, the oncogenic potential of Permethrin was very weak. The possibility of oncogenic potential in man was extremely remote." [quoted from the memorandum by Philip Gray, Jr., dated March 20, 1981.]²

Regarding this "advisory opinion," it was recalled that the Agency did not have Guidelines for Carcinogen Risk Assessment at that time. These guidelines were promulgated in 1986. Also, with the exception of some recently

1 Should be B-W

2 This 1981 Panel report cites both the FMC I and FMC II mouse studies as being inadequately conducted, and that ". . . none of the available studies provide for . . . a [dose-response] curve."

The Peer Review Committee agreed that the FMC I mouse study was improperly conducted (and therefore invalid). The FMC II mouse study was, however, found to be adequately conducted and provided convincing evidence of oncogenicity in the female mouse, in which lung adenomas, especially, occurred with a clear dose-response.

submitted historical control data relating to the FMC Mouse II study, it was observed that the toxicological data base for permethrin had not appreciably changed since 1981.

In reviewing the SAP's recent 1989 comments, it was apparent that the panel considered only one oncogenicity study to be clearly positive for tumors. This was the FMC Mouse II study in which a dose-response was manifested in lung tumors in the female mice (both adenomas and carcinomas). The SAP did not indicate concern with the findings in any of the other five oncogenicity studies on permethrin. Noting that permethrin was not mutagenic in a battery of bioassays, the SAP recommended Group C classification and no quantitative risk assessment because of the "relatively weak tumorigenicity and the lack of [positive] mutagenicity data." There was no further discussion or elaboration by the SAP.

The Peer Review Committee took the SAP recommendations under advisement, but continued to have serious concerns regarding further findings in the FMC Mouse II study and in several of the other studies on permethrin. In particular, in the absence of new information or convincing rationale to the contrary, the committee again concluded that in addition to the statistically significant increase in lung adenomas and carcinomas (both dose-related) in the female mice in the FMC Mouse II study, the same study also indicated statistically significant increases in liver adenomas in both female mice and male mice. Additionally, in the B-W mouse study, a significant increase in lung adenomas (within the historical control range) was observed in female mice at the highest dose and in the ICI mouse study a slight increase in lung adenomas (not statistically significant) was observed in the male mice at the highest dose.

With respect to the rat studies, although two studies on Wistar strain rats presented no evidence of carcinogenicity, there was nevertheless equivocal evidence of increased lung tumors in male rats in the third (FMC) rat study on Long-Evans strain rats and the committee again noted that female rats probably had not been tested at high enough dosage levels in any of the three studies.

The increased incidences of lung adenomas in the B-W and ICI mouse studies and of lung tumors in the FMC rat study provided supportive evidence of the lung being a target organ for permethrin and contributed to the committee's decision to recommend a quantitative risk assessment based on lung tumors. In addition, some supportive SAR information (the induction by cypermethrin of increased lung tumors in female mice and by bifenthrin of increased lung tumors in female mice and increased liver and bladder tumors in male

mice) and some unresolved genotoxicity issues also contributed to the decision to call for a quantitative risk assessment.

Considering all of the above, the majority of the committee members felt that the overall weight-of-the-evidence continued to support a Group C classification and that a quantitative risk assessment was still warranted. A few persons, on the other hand, argued against the call for a quantitative risk assessment. In essence, these persons concurred with the viewpoints and recommendations made by the SAP in 1981 and again in 1989.

E. Conclusions:

The Peer Review Committee, by majority vote, reaffirmed its prior classification of permethrin as a Group C carcinogen (possible human carcinogen) and again recommended that a quantitative risk assessment be performed. It was also confirmed that the quantitative risk assessment should be based on data from the FMC Mouse II study on CD-1 strain mice and more specifically on the dose-related increase in combined lung adenomas and/or carcinomas observed in the female mice in this study.



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